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(54) **Compositions of crosslinkable prepolymers for use in therapeutically active biodegradable implants**

(57) The invention provides a composition suitable for preparing a therapeutically-active biodegradable implant, comprising at least one crosslinkable multifunctional prepolymer having at least two polymerizable end groups and at least one biologically-active component, the said composition having a viscosity such that it is deformable at a temperature between 0°C and 60°C, more preferably between 15°C and 40°C into a three-dimensional shape and being hardenable by crosslinkage within the said temperature range.

The invention further provides crosslinkable multifunctional prepolymers suitable for such a composition, comprising a biodegradable region made from a polyacetal and/or from an amorphous lactone-derived copolyester and/or comprising a hydrophilic region, as well as methods for producing such prepolymers.

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Descripti n

[0001] The present invention is in the field of therapeutically active biodegradable implants. More specifically, the invention relates to a class of crosslinkable polyester, polyorthoester or polyacetal prepolymers for use in the manufacture of such implants, as well as to specific biologically-active crosslinkable polyester, polyorthoester or polyacetal formulations and to implants obtained by crosslinking such formulations. The present invention further refers to a method for repairing bone defects in a mammal while making use of these polyester, polyorthoester or polyacetal prepolymers and formulations.

BACKGROUND OF THE INVENTION

[0002] Biodegradable polymers are widely used nowadays and have been designed for a broad range of medical applications and devices like implants in order to fulfill a temporarily mechanical function, such as for bone plates, sutures and the like and/ or to deliver a drug locally in a controlled manner. In such applications, an implant material with an appropriate strength is required in order to provide a temporarily bridge in the bone defect.

[0003] In particular with respect to mechanical medical devices, a method is already known whereby cells having a desired function are grown on a prefabricated polymer scaffold, followed by transfer of the cell-polymer scaffold into a patient at a site appropriate for attachment in order to produce a functional organ equivalent. Success of this procedure mostly depends on the ability of the implanted cells to attach to the surrounding environment and to stimulate angiogenesis. The polymer scaffolding used for the initial cell culture is made of a material which degrades over time and is therefore no longer present in the chimeric organ. The preferred material for forming the matrix structure usually is a biodegradable synthetic polymer such as polyglycolic acid, polyorthoester, polyanhydride or the like, which is easily degraded by hydrolysis. This material may be overlaid with a second material such as gelatine or agarose in order to enhance cell attachment. In the case of making a cartilageneous structure, such a procedure is described namely in U.S.Patent No. 5,041,138 making specific mention of polyglactin, a 90 :10 copolymer of glycolide and lactide marketed by Ethicon Co. (Somerville, New-Jersey) under the trade name Vicryl®. The polymer matrix must provide an adequate site for attachment and adequate diffusion of nutrients and/or growth factors supplied during cell culture in order to maintain cell viability and growth until the matrix is implanted and vascularization has occurred. A preferred structure for organ construction therefore is a structure formed of polymer fibres having a high surface area which results in a relatively low concentration gradient of nutrients to achieve uniform cell growth and proliferation. Obviously a disadvantage of this kind of method is that the shape of the prefabricated polymer scaffold can hardly be changed at the time of implanting it into the patient.

[0004] Among biodegradable polymers, special attention has been paid to polyesters and copolyesters, especially those based on lactones such as ε-caprolactone, glycolide and lactides. In particular, the controlled release of bioactive agents from lactide/glycolide polymers is described in U.S.Patent No. 3,773,919 and by D.H.Lewis in *Biodegradable Polymers in Drug Delivery Systems,* ed. M.Chasin, R.Langer, Marcel Dekker, New-York, p.1-41. S.J.Holland et al. in *J.Controlled Release* (1986) 4 :155-180 also disclosed the potential of polyesters as controlled macromolecular release system. For instance, the controlled release of a Luteinizing hormone releasing hormone (LHRH) analogue from poly (d,l-lactide-co-glycoside) microspheres is discussed by L.M.Sanders et al. in *J.Pharm.Sci.* (1984) 73, No.9. More specifically, U.S.Patent No. 4,902,515 discloses encapsulating a biologically active ingredient in interlocked segments of poly(R-lactide) and poly(S-lactide) at a temperature below the melting temperature of the highest melting crystalline phase in the presence of the said biologically active ingredient until interlocking occurs.

[0005] Suitable polymer implants, in particular polyester implants, can be conventionally prepared while using biodegradable polymeric compositions obtained by solvent casting, filament drawing, meshing, extrusion-molding or compression-molding. Therapeutically active implants can similarly be prepared by dispersing a drug into a polymer matrix and then extruding the resulting mixture. Due to the usually high temperatures necessary for extruding polymers, such a procedure is obviously mainly limited to biologically active drugs with a substantially high thermal stability. This procedure is therefore not easily applicable to thermally degradable drugs such as most peptides and proteins. In many cases, the active forms of proteins are difficult to formulate together with biodegradable polymers. Biodegradable hydrogels, such as polyacetals hydrogels, can be used to deliver macromolecular therapeutic agents, e.g. as disclosed in U.S.Patent No. 4,713,441, including proteins, however the delivery of the protein to the systemic and local system is relatively rapid and is determined primarily by the rate of dissolution of the protein particles, thus providing limited utility for a sustained, controlled release of the drug.

[0006] WO 99/03454 discloses a method for delivering a biologically-active substance such as a protein (including a bone morphogenetic protein or a transforming growth factor), comprising polymerizing a mixture of the said biologically-active substance and of a macromer to form articles, and then administering said articles to a mammal, wherein polymerization takes place in the absence of a polymerizable monovinyl monomer. By « macromer « in this document is meant a three-component polymer comprising (1) a biocompatible, water-soluble region e.g. forming a central core

or backbone, (2) a (preferably at least two) biodegradable/hydrolysable region(s) e.g. attached to the water-soluble region and (3) at least two polymerizable regions or end groups attached to the degradable region and/or the water-soluble region. For instance, the water-soluble region may consist of a poly(ethylene glycol), the degradable region may consist of 4 to 6 lactate or caprolactone groups and the polymerizable regions may consist of acrylate groups. According to this document, the rate of release of the particles including the biologically active substance is independent of particle size, whereas the particles have a mean diameter of 50 nm to 1 mm. Preferably, the articles are administered to the lung or intravenously, subcutaneously, intramuscularly, orally or nasally. They may also be shaped to fit into a specific body cavity.

[0007] U.S.Patent No. 5,801,033 discloses mixing a biological material selected from tissue cells, subcellular organelles and subcellular non-organelle components together with an aqueous solution comprising a photoinitiator and a macromer comprising a water-soluble polymer having at least two sites of unsaturation (e.g. an ethylenically unsaturated derivative of polyethylene oxide or polyethylene glycol), forming geometric shapes from the resulting mixture, and polymerizing the macromer by exposing the geometric shapes to light radiation to form an encapsulating membrane surrounding the biological material.

[0008] None of the above-mentioned documents is concerned with tailoring a biological material to the specific physico-chemical requirements, in particular the viscosity characteristics, encountered when a synthetic load-bearing (e.g. a hip) or non load-bearing (e.g. a cronal fracture) therapeutically active biodegradable bone implant is to be hardened *in situ* at the place where bone growth is expected. Consequently there is a need for the design of specific biocompatible crosslinkable polymers and formulations containing them, in particular the design of polymers formulations having specific viscosity characteristics and crosslinking ability between room temperature and body temperature, within which thermally degradable macromolecular biologically-active ingredients such as peptides or proteins can be easily dispersed and which can be suitably hardened within a short period of time at moderate temperatures, e.g. near the body temperature of warmblooded animals such as mammals, while being able to be formulated with a wide range of other additives suitable for use in implant materials for the healing of bone defects.

SUMMARY OF THE INVENTION

[0009] In view of the above-mentioned problem, which to the best of our knowledge has not yet been properly solved, the present invention is based on the unexpected discovery that difficulties in using biodegradable polymers for effectively repairing bone defects in mammals, especially in humans, horses, dogs, bovines and the like, can be overcome by a proper selection of the polymer components in order to meet both the physico-chemical, in particular viscosity, requirements of medical procedures such as the *in situ* bone implant technology and the compatibility with a wide range of biologically active additives which may most often be used in order to improve the chances of success of such procedures. Therefore, in a first aspect, the present invention provides a composition comprising at least one crosslinkable multifunctional prepolymer having at least two polymerizable end groups and at least one biologically-active component, the said composition having a viscosity such that it is deformable at a temperature between about 0°C and 60°C, more preferably between 15°C and 40°C into a three-dimensional shape and being hardenable by crosslinkage within the said temperature range, the said crosslinkable multifunctional prepolymer preferably comprising at least one of a polyester, a polyorthoester or a polyacetal. and the said composition being suitable for the preparation of a therapeutically-active biodegradable implant, especially for *in situ* bone repair. In a second aspect, the present invention provides a biodegradable crosslinkable multifunctional prepolymer or macromer having at least two polymerizable end groups, wherein the biodegradable region thereof is substantially amorphous, the said prepolymer being suitable for the manufacture of therapeutically-active biodegradable formulations to be used for implants, such a prepolymer being for instance a polyester sequence prepared from a mixture of lactones in suitable amounts, or a polyorthoester or a polyacetal. In a third aspect, the present invention further provides specific biodegradable crosslinkable multifunctional prepolymers or macromers such as for instance including a hydrophilic sequence and/or including a polyacetal degradable sequence, biologically-active formulations comprising said macromers and their use for making therapeutically-active biodegradable implants by crosslinking such formulations at moderate temperatures. In a fourth aspect, the present invention features a method for making a therapeutically-active biodegradable implant including the steps of (a) combining at least one specific biodegradable crosslinkable multifunctional prepolymer or macromer having at least two polymerizable end groups, such as one including a predominantly amorphous biodegradable region and/or a hydrophilic sequence and/or or a biodegradable polyacetal sequence, together with at least one biologically-active component and optionally at least one additive selected from bioactive component delivery systems, biocompatible unsaturated functional monomers, biocompatible degradable porosity-inducing components and polymerization initiators so as to provide a viscous but still flowable liquid mixture, (b) implanting the said mixture into the body of a mammal at a place suitable for growth and (c) exposing the said implanted mixture to conditions suitable for crosslinking the biodegradable crosslinkable multifunctional prepolymer and optionally the biocompatible unsaturated functional monomers within a reasonable period of time at a moderate temperature, for instance a temperature of between 0°C and

60°C, preferably between room temperature, e.g. 15°C, and about 40°C. In a fifth aspect, the present invention provides a method for repairing a bone defect by implanting a bone repair low viscosity formulation based on such a specific biodegradable multifunctional crosslinkable prepolymer or macromer into the body of a mammal, namely a human, a horse, a dog, a bovine or the like, at a place suitable for bone growth and further crosslinking the said formulation by suitable means such as light and/or moderate temperature until hardening takes place.

DETAILED DESCRIPTION OF THE INVENTION

[0010] The present invention will be described with reference to certain embodiments but the invention is not limited thereto but only by the appended claims.

[0011] The present invention is based on the achievement of a desirable viscosity for a combination of a crosslinkable multifunctional prepolymer having at least two polymerizable end groups (hereinafter referred to as a « macromer » or a telechelic-type polymeric precursor), for instance based on a polyester, a polyorthoester or a polyacetal, with at least one biologically-active substance such as a peptide or a protein (including a bone morphogenetic protein or a transforming growth factor), optionally chemically modified in order to contain polymerizable groups, and possibly other compatible additives (such as calcium phosphate, bioceramics, bioglass, macroporous polymers e.g. containing ethylenically unsaturated functional units such as for instance 2-hydroxyethyl methacrylate, vinylphosphonic acid, acrylic acid, methacrylic acid, crotonic acid and the like), suitable for manufacturing a therapeutically active implant, especially a bone implant, the said combination being hardenable under mild conditions, such as a temperature between abut 0°C and 60°C, more preferably between about 15°C and about 40°C, by crosslinking the said macromer through its (usually unsaturated) polymerizable end groups. The term « desirable viscosity » as used herein, unless otherwise stated, means a viscosity such that the formulation is deformable at moderate temperatures (e.g. between about 0°C and 60°C, particularly between about 15°C and about 40°C), for example by hand, by syringe or by any other suitable surgical instrument, into a three-dimensional shape. Macromers suitable for performing the present invention may be designed in a number of different ways, as will be further explained below, provided that they contribute in a biodegradable composition that, due to its desirable viscosity, can be easily implanted and hardened at a moderate temperature into the body of a mammal, i.e. preferably applied to a bone component of a mammal and more preferably poured or injection-molded into a bone cavity of a mammal such as a human, a horse, a dog, a bovine or the like. These different ways of achieving the desired result may be combined in the design of a macromer of the invention, if necessary.

[0012] The term « macromer « as used herein, unless otherwise stated, means an at least two-components prepolymer comprising (1) at least one biodegradable region and (2) at least one, preferably two or more, polymerizable region(s) and optionally (3) a hydrophilic region. Preferably, the biodegradable region of the first macromer is biocompatible and forms the central core or backbone to which is (are) attached one or, more preferably, at least two polymerizable region(s) consisting of polymerizable end groups. This said macromer may be polymerized to form a network which can be formulated with suitable additives for successful implantation into the body, preferably into bone cavities, of a mammal such as a human, a horse, a dog, a bovine or the like. An important aspect of the macromer of the invention is that the polymerizable regions are separated by at least one biodegradable region in order to facilitate uniform degradation *in vivo*. The macromers used in the present invention may be constructed in various ways. For instance, in one embodiment, a central hydrophilic region has at least two biodegradable regions attached to it with at least two polymerizable regions attached to the said biodegradable regions so that, upon degradation, the polymerizable regions in their polymerized gel form become separated. Furthermore, it should be understood that in each of the above-described modes of construction, the number of biodegradable regions and/or polymerizable regions and/or hydrophilic regions is not limited to two but may be three, four or even more, thus resulting in branched, grafted, star-shaped and/or comb-shaped structures.

[0013] Although the present invention is based on the use of a prepolymer or macromer, such as herein above described, for instance based on a polyester, a polyorthoester or a polyacetal, the invention is not limited to using this macromer alone. Indeed, the said first macromer may be used in combination with at least one second macromer already conventional in the art. The term « second macromer « as used herein, unless otherwise stated, means a prepolymer comprising at least one, preferably two or more, polymerizable region(s). As will readily be appreciated by those skilled in the art, the first macromer and the second macromer(s) may be combined in any proportion, provided that the addition of the second macromer(s) does not result in an alteration of the viscosity and/or the crosslinkability at moderate temperature which would make the combination unsuitable for the purpose of the present invention.

[0014] In order to obtain a biodegradable material with a viscosity suitable for the manufacture of implants, such as specified hereinbefore, it is most preferred that the average number molecular weight of the crosslinkable macromer of this invention (as determined by gel permeation chromatography according to standards and procedures well established in the art) be in the range of about 200 to about 20,000, preferably from about 2,000 to 6,000 and more preferably from about 2,500 to 5,000. If necessary, the viscosity of the biodegradable material may however be adjusted

by formulating the crosslinkable macromer with a suitable amount of a viscosity regulator such as a monomer, as explained hereinafter.

[0015] The chemical constitution of each component of the macromer such as above-defined will now be explained in further details.

[0016] One of the building components for the preparation of a prepolymer with a hydrophilic region may be a polyether polyol with two or more hydroxyl groups derived from polyethylene glycol or a copolymer of ethylene oxide and propylene oxide. For instance the sequence forming the hydrophilic regions may be represented by the formula - O - R - O - , wherein R may be an alkylene group possibly substituted with one or more hydroxy groups or alternatively R may be

$$-(CH_2 - CH_2 - O)_n - (\underset{\substack{| \\ R'}}{C}H - CH_2 - O)_{n'},$$

wherein R' is methyl or a higher order alkyl chain and n is from 1 to about 200, more preferably 1 to 10 and n' is 0 to about 100, preferably 0 to 20.

[0017] Examples of polyol intitiators suitable for the preparation of the prepolymer of the present invention include for instance low molecular weight polyols (i.e. having a molecular weight of not more than about 300, preferably not more than 150) such as e.g. ethylenediol, propanetriol (glycerol), butanediol-1,4 (tetramethyleneglycol), propanediol-1,3 (trimethylene-glycol), pentanediol-1,5 (penta-methyleneglycol), hexanediol-1,6, diethyleneglycol, triethyleneglycol, tetra-ethyleneglycol, pentaerythritol, propylene glycol, pentaerythritol, dipentaerythritol and the like. As will readily be understood by those skilled in the art, the above list should not be considered as limiting the scope of the invention. Preferably when the biodegradable region of the macromer used in the present invention is suitably selected as a predominantly amorphous region, as explained hereinafter, then the polyol initiatior for the preparation of the prepolymer of the present invention may be a medium or high molecular weight polyol sequence. By « medium or high molecular weight polyol sequence » as used herein, unless otherwise stated, it is meant a polyol sequence having a molecular weight of at least about 400 and possibly up to about about 10,000.

[0018] As is well known to those skilled in the art, a suitable polymer sequence for the biodegradable region of the macromer of the present invention may be a poly-α- hydroxyacid, a polyester sequence (e.g. a polylactone), a polyaminoacid, a polyanhydride, a polyorthoester, or a mixture of these polymers. It may also be a polyacetal sequence. A first class of preferred biodegradable polymer sequences consists of polymers and copolymers (whether random, block, segmented or grafted) of lactones such as ε-caprolactone, glycolide, L-lactide, D-lactide, mesolactide, 1,4-dioxan-2-one, trimethylene carbonate (1,3-dioxan-2-one), χ-butyrolactone, δ-valerolactone, 1,5-dioxepan-2-one, 1,4-dioxepan-2-one, 3-methyl-1,4-dioxan-2,5-dione, 3,3 diethyl-1,4-dioxan-2,5-one, ε-decalactone, pivalolactone and 4,4-dimethyl -1,3-dioxan-2-one and the like. Several embodiments of such copolymers have been described by, among others, U.S.Patent No. 5,951,997, U.S.Patent No. 5,854,383 and U.S.Patent No. 5,703,200 and shall therefore be considered as being within the scope of the present invention. More particularly preferred for carrying out the present invention are non-crystalline, low crystallinity or predominantly amorphous lactone copolymers, especially copolymers of two or more lactones wherein none of the lactone comonomers is present in the resulting copolymer in a molar proportion above about 70%. As usual, crystallinity for the purpose of this embodiment of the present invention shall be measured by X-ray diffractometry, while using test methods and apparatus well known to those skilled in the art. The terms « low crystallinity » or «predominantly amorphous » as used herein, unless otherwise stated, shall mean a degree of crystallinity (as measured as above mentioned) not exceeding about 50%, preferably not exceeding 15% and more preferably not exeeding about 5%.

[0019] A second class of preferred biodegradable polymer sequences for the macromer used in the present invention consists of hydroxy-terminated polyorthoesters obtainable for instance by the addition reaction of a diol (e.g. an alkyl diol such as ethylenediol, trimethyleneglycol, tetramethyleneglycol, pentamethyleneglycol, hexanediol-1,6 and the like, or a cycloalkyl diol such as 1,4-cyclohexanedimethanol or 1,4-cyclohexanediol) or polyethyleneglycol onto a diketene acetal. Such a synthesis method for a hydroxy-terminated polyorthoester is well known in the art and was namely described, for instance starting from 3,9-bis(ethylidene-2,4,8,10-tetraoxaspiro[5,5]undecane, by J.Heller et al. in *Macromolecular Synthesis* 11 :23-25.

[0020] Yet another class of preferred biodegradable polymer sequences for the macromer used in the present invention consists of hydroxy-terminated polyacetals obtainable for instance by the condensation reaction of at least a diol (such as hereinabove mentioned) and a divinylether. Various embodiments of such a method for making a hydroxy-terminated polyacetal are well known in the art. For instance, U.S.Patent No. 4,713,441 describes unsaturated, linear, water-soluble polyacetals having molecular weights from about 5,000 to about 30,000 which may be formed by condensing, for instance in a polar solvent such as tetrahydrofuran and in the presence of an acidic catalyst such as

paratoluenesulfonic acid, a divinylether, a water-soluble polyglycol and a diol having a (preferably pendant) unsaturation and which may be further converted to hydrogels, for instance by using a free-radical initiator in order to copolymerize the double bonds in the polyacetal with a monomeric compound having a reactive double bond. Another typical procedure for this kind of polyacetals may be found in Heller et al., *Journal of Polym.Science, Polym.Letters Edition* (1980) 18:293-7, starting from 1,4-divinyloxybutane or diethyleneglycol divinylether. French patent No. 2,336,936 further refers to crosslinked polyacetals formed by condensing diols or polyols with 3,4-dihydro-2H-pyran-2-ylmethyl-3,4-dihydro-2H-pyran-2-ylcarboxylate.

[0021] One way of obtention of polyacetals useful within the scope of the present invention may be generalized as follows :

$$x\ HO-R_1-OH\ +\ y\ CH_2=CH\text{-}O\text{-}R_4\text{-}O\text{-}CH=CH_2 \longrightarrow HO-[R_1-O-\underset{\displaystyle CH_3}{CH}\text{-}O\text{-}R_4\text{-}O\text{-}\underset{\displaystyle CH_3}{CH}\text{-}O]_z-R_1-OH$$

wherein R_1 is a sequence of 2 to 20 methylene units and R_4 is a sequence of 2 to 20 methylene units or is represented by the formula

$$\text{-}(\text{-}CH_2CH_2O\text{-})_m\text{—}(\text{-}CH_2\underset{\displaystyle CH_3}{CH}O\text{-})_p\text{-}$$

wherein each of m and p is from 0 to 1,000 provided that the sum m+p is from 1 to 1,000.

[0022] An alternative method for obtaining polyacetals useful within the scope of the present invention is for instance as follows :

$$x\ HO-R_1-OH\ +\ y\ R_2-O-\underset{\displaystyle R_3}{CH}-R_4 \quad HO\ \text{-}[-R_1-O-\underset{\displaystyle R_3}{CH}-O\text{-}]_z\text{-}R_1-OH$$

wherein R_1 is a sequence of 2 to 20 methylene units and each of R_2 and R_3 independently represents an alkyl or alkylaryl group and x > y, the ratio x/y determining the polymerization degree z.

[0023] The polymerizable region(s) of the crosslinkable multifunctional macromer used in the present invention contain polymerizable end groups such as ethylenic and/or acetylenic unsaturations, preferably carbon-carbon double bonds, capable of polymerizing the said macromer, optionally together with other unsaturated monomers which may be present in the composition, under suitable conditions as decribed hereinafter. The choice of suitable polymerizable groups will be dictated by the need for rapid polymerization and gelation. Therefore, namely because they can be polymerized while using various polymerization initiating systems, as discussed below, acrylate, methacrylate, acrylamide and methacrylamide groups are preferred.

[0024] The crosslinkable multifunctional prepolymers or macromers used in the present invention can be manufactured by different methods, some of them being detailed hereinafter without a pretention to exhaustivity. A first method will be explained by reference to macromers based on polylactones and comprises polymerizing a lactone or copolymerizing a mixture of lactones, preferably a mixture wherein none of the lactones is present in a molar proportion above about 70% (as stated above), at a temperature between about 120°C and 180°C in the presence of at least a polyol (such as previously described), the said polyol preferably being in a controlled molar excess with respect to the said mixture of lactones, and further in the presence of at least a lactone polymerization catalyst, for instance a transition metal carboxylate such as zinc diacetate or tin dioctoate, or any alternative catalyst known to those skilled in the art. This type of copolymerization method is able to provide random copolymers as well as copolymers comprising block sequences, depending on the comonomer composition and ratio as well as on the operating conditions, as is well known to those skilled in the art. For the purpose of the present invention, it is usually preferable that the polyol(s) be used in a molar ratio, with respect to the lactone(s), of not more than about 1 :10, more preferably not more than about 1 :20. After this polymerization step, and possibly after a step for removing the polymerization catalyst from the polyester diol obtained, the latter is further reacted with a monomer containing at least one ethylenic or acetylenic unsaturation such as a vinyl group, for instance an acrylic monomer. The said acrylic monomer may be any acrylic monomer reactive

with the terminal hydroxy groups of the polyester diol, such as acrylic or methacrylic acid (in which case the molar ratio acrylic: polyester should be at least 2) or methacrylic anhydride (then the molar ratio acrylic : polyester should be at least 1). This acrylation step may carried out in the presence of a suitable solvent such as methylene chloride and possibly further in the presence of at least a catalyst for the acrylation reaction, for example a tertiary amine such as 4,N-dimethylaminopyridine, triethylamine or the like.

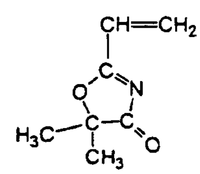
[0025] An alternative method for preparing crosslinkable multifunctional prepolymers or macromers used in the present invention involves anionically polymerizing a lactone or copolymerizing a mixture of lactones, preferably a mixture wherein none of the lactones is present in a molar proportion above about 70% (as stated above), at a temperature below about 30°C in the presence of an aprotic solvent, for instance tetrahydrofuran or the like, and further in the presence of at least an alcaline metal alkoxide of a selected alcohol and an anionic polymerization catalyst such as an alcaline metal alkoxide of a tertiary alcohol (e.g. sodium, potassium or cesium tertiary butoxide) and/or a crown-ether such as 1,4,7,10,13,16-hexaoxocyclooctane (18 crown-6). As is well known in the art, such a polymerization method can take place at very low temperatures, i.e. down to about-78°C. Preferred alcaline metal alkoxides as co-reactants with the lactone(s) include sodium and potassium methoxylates. During or after this anionic polymerization step, a monomer containing at least one ethylenic or acetylenic unsaturation such as a vinyl group, for instance an acrylic monomer (such as contemplated hereinabove), is added to the reaction mixture in order to perform the final step, preferably an acrylation step, leading to formation of the crosslinkable macromer.

[0026] Yet an alternative method for preparing a crosslinkable multifunctional polyorthoester prepolymer or macromer used in the present invention comprises polymerizing a diketene acetal or copolymerizing a mixture of diketene acetals in the presence of at least one polyol, the alcohol groups preferably being in a molar excess with respect to the ketene acetal groups, and of at least a ketene acetal polymerization catalyst and, possibly after a step for removing the catalyst from the (co)polymer obtained, reacting the hydroxyl end groups of the latter with a monomer containing at least one ethylenic or acteylenic unsaturation, for instance a vinyl group, such as an acrylic monomer (as defined hereinabove).

[0027] Yet an alternative method for preparing a crosslinkable multifunctional polyacetal prepolymer or macromer used in the present invention comprises polymerizing a divinylether derivative or copolymerizing a mixture of divinylether derivatives in the presence of at least one polyol, the alcohol groups preferably being in a molar excess with respect to the vinylether groups, and of at least a vinylether polymerization catalyst and, possibly after a step for removing the catalyst from the polymer obtained, reacting the hydroxyl end groups of the latter with a monomer containing at least one ethylenic or acetylenic unsaturation, for instance a vinyl group, such as an acrylic monomer (as defined hereinabove). In this embodiment alike in the previous embodiment, it is preferred that the molar ratio of alcohol groups (originating from the polyol) to the ketene acetal or vinylether is in a controlled excess of between about 0.1% and 30%, more preferably from 1% to 5%.

[0028] Methods for attaching the polymerizable region(s) to the degradable region(s) of the crosslinkable macromer used in the present invention are conventional in the art. In addition to the specific embodiments described hereinabove with respect to polycaprolactones, it is worthwhile making a specific mention of the attachment of an acrylamide or a methacrylamide end group by reacting the terminal hydroxy groups of, for instance, a biodegradable polymeric sequence such as a polyacetal with at least an unsaturated azlactone, preferably a 2-alkenyl azlactone. The term « azlactone » as used herein, unless otherwise stated, means an α-acylaminoacid anhydride such as for instance containing the 2-oxazolin-5-one or the 2-oxazin-6-one functional unit. Most preferred 2-alkenyl azlactones include these wherein the alkenyl group has from 2 to 20 carbon atoms, in particular:

- vinylazlactones such as 2-vinyl-4,4-dimethyl-2-oxalin-5-one (available from SNPE, Inc., Princeton, New Jersey) represented by the following formula :



- 2-isopropenyl-4,4-dimethyl-2-oxalin-5-one, 2-vinyl-4-ethyl-4-methyl-2-oxalin-5 -one and the like such as disclosed in U.S.Patent No. 4,305,705.

[0029] As is well known to those skilled in the art, the azlactone heterocycle is highly reactive with hydroxy nucleophiles and will therefore provide the unsaturated amide group under suitable reaction conditions.

[0030] Thanks to any of the above-mentioned specific designs of the macromer used in the present invention, and/

or by selecting a mixture of lactones for achieving an amorphous biodegradable region and/or by selecting a molar ratio polyol(s):lactone(s) of not more than about 1 :100, preferably 1 : 10 and/or by selecting a biodegradable polyacetal sequence, it becomes possible to obtain a composition having a suitable viscosity which is useful for the manufacture of a therapeutically-active biodegradable implant.

[0031] The present invention provides biologically-active formulations based on the above described crosslinkable macromers in admixture with biocompatible additives suitable for the intended therapeutic use, in particular for the preparation of load-bearing and non load-bearing *in situ* hardenable implants. In particular, it is within the scope of this invention to incorporate one or more medico-surgically useful substances into said formulations, in particular those which are able to accelerate or beneficially modify the healing process when the formulations are applied *in vivo* at a bone repair site. For example, the formulations of this invention include at least one biologically-active component, preferably in a biologically effective amount, such as a therapeutic, diagnostic or prophylactic agent. The therapeutic agent can be selected for its antimicrobial properties, capability for promoting repair or reconstruction of bone and for specific indications such as thrombosis. These include for instance antimicrobial agents such as broad spectrum antibiotics for combating clinical and sub-clinical infections at the bone repair site, for example gentamycin, vancomycine and the like. Other therapeutic agents which can be considered for incorporation into the formulations of this invention are naturally occurring or synthetic organic or inorganic compounds well known in the art, including proteins and peptides (produced either by isolation from natural sources or recombinantly), hormones, bone repair promoters, carbohydrates, antineoplastic agents, antiangiogenic agents, vasoactive agents, anticoagulants, immunomodulators, cytotoxic agents, antiviral agents, antibodies, neurotransmitters, oligonucleotides, lipids, plasmids, DNA and the like. More specifically, bone repair promoters which can be present in the formulations of this invention include bone growth factors, bone morphogenetic proteins, transforming growth factors and the like. Therapeutically active proteins which can additionally be present in the formulations of this invention include, without any specific limitation, fibroblast growth factors, epidermal growth factors, platelet-derived growth factors, macrophage-derived growth factors such as granulocyte macrophage colony stimulating factors, ciliary neurotrophic factors, cystic fibrosis regulator genes, tissue plasminogen activator, B cell stimulating factors, cartilage induction factor, differentiating factors, growth hormone releasing factors, human growth hormone, hepatocyte growth factors, immunoglobulins, insulin-like growth factors, interleukins, cytokines, interferons, tumor necrosis factors, nerve growth factors, endothelial growth factors, non-steroidal anti-inflammatory drugs, osteogenic factor extract, T cell growth factors, tumor growth inhibitors, enzymes and the like, as well as fragments thereof.

[0032] Diagnostic agents which can be present in the biologically-active formulations of this invention include, without any specific limitation, conventional imaging agents (for instance as used in tomography, fluoroscopy, magnetic resonance imaging and the like) such as transition metal chelates. Such agents will be incorporated into the formulations of the invention in an effective amount for performing the relevant diagnostic.

[0033] The biologically-active formulations of this invention may additionally include at least one biologically-active component delivery system of a nature and in an amount known to be suitable for the manufacture of an implant, in particular a bone implant, such as for instance demineralized bone powder, hydroxyapatite powder or particles, coral powder and/or resorbable calcium phosphate particles. The formulations may also include an effective amount of at least a degradable biocompatible porosity-inducing component, such as a porous gelatine (preferably with a particle size from about 50 to 300 μm) a carbohydrate, a gelatine derivative containing polymerizable side groups (in this case, the formation of an interpenetrating network with the macromer becomes possible) or porous polymeric particles. The latter may be made for instance from acrylic copolymers comprising e.g. one or more alkyl methacrylates, 2-hydroxyethyl methacrylate and possibly acids such as acrylic acid, methacrylic acid, vinylphosphonic acid, crotonic acid and the like). While inducing porosity, these additives will stimulate angiogenesis. By complexing calcium ions, they may also promote calcium phosphate deposition and hence bone formation.

[0034] The biologically-active formulations of this invention may additionally include at least one ligand with affinity for surrounding cells such as, in particular, mesenchymal cells. More specifically, the said ligand may be a sequence, a fragment or a derivative of a natural extracellular matrix protein like fibronectin or vitronectin which is able to mediate adhesion of cells to each other and to their surroundings and to transduce signals across the cell membrane, via binding and releasing integrins, thus leading to changes in gene expression, cell behavior and differentiation. For instance fibronectin is a glycoprotein which may be found in the extracellular matrix (where it is in the form of insoluble fibrils) and in blood plasma (as a soluble dimer) and which can mediate interactions between cells and extracellular matrix. Fibronectin can also bind to other matrix components such as collagen and heparin and to specific cell surface receptors. The ligand included into the biologically-active formulations of this invention may be an oligopeptide present in such natural proteins, such as the tripeptide RGD (arginine-glycine-aspartic acid), the tetrapeptide RGDS (meaning RGD-serine) or the like. As is well known to those skilled in the art, RGD is found in the integrin-binding domains of a number of ligands, and sequences flanking this tripeptide are presumed to determine the exact binding specificity. For a better affinity with surrounding cells and a better compatibility with the other components of the biologically-active formulations of this invention, the said ligand may further be chemically modified, for instance by the inclusion of un-

saturated polymerizable groups, preferably of the same nature as the unsaturated end groups of the crosslinkable macromer, for instance by N-methacryloylation. In this case, the additive can be covalently anchored onto the biodegradable matrix and will not be easily leachable, unless after degradation of the matrix. Such incorporated peptide sequences (optionally chemically modified) are able to contribute to the angiogenesis process and to the cell ingrowth process and therefore lead to improved bone formation. The ligand may also be modified by incorporating it into a suitable biologically inert polymer material serving as a hydrophilic coating. An example of such a coating polymer material is poly-N-2-hydroxypropylmethacrylamide and related copolymers such as disclosed for instance in WO98/19710. The biologically-active formulations of this invention may additionally include one or more biopolymers such as hyaluronic acid, chondrointinsulfate, dermatansulfate and the like. These biopolymers can again be chemically modified (such as previously mentioned for gelatine derivatives and for ligands), e.g. by reaction with (meth)acrylic anhydride or with azlacton, so that they will contain polymerizable side groups. During the crosslinking/hardening step of the composition according to the present invention, these biopolymers can then be covalently anchored onto the biodegradable matrix.

[0035] The biologically-active formulations of this invention may additionally include one or more biocompatible unsaturated, preferably ethylenically unsaturated, functional monomers, more preferably functional acrylates and/or methacrylates such as hydroxyalkyl methacrylates (in paticular 2-hydroxyethyl methacrylate or hydroxypropyl methacrylate) or vinylphosphonic acid for the purpose of either further adapting the viscosity of the crosslinkable formulation to the specific need of the implant or further increasing the strength of the final crosslinked formulation by participating in the crosslinking process at moderate temperature together with the multifunctional macromer. The choice of suitable functional monomers for this purpose depends on the viscosity and crosslinkability of the formulation to be achieved and is well within the knowledge of those skilled in the art of acrylic monomer formulation. The amount of such unsaturated functional monomer to be incorporated into the formulation of the invention is an effective amount for performing the desired viscosity-adaptation or strength-increase.

[0036] Finally, the biologically-active formulations of the present invention may additionally include one or more polymerization initiators that are capable of polymerizing the crosslinkable macromer under the influence of light and/or redox systems that are capable of polymerizing the crosslinkable macromer through radical initiation, possibly under the influence of temperature. When polymerization is to take place under the influence of light, for instance light having a wavelength of at least about 300 nm, polymerization photoinitiators which can be used include heterocyclic compounds, for instance xanthines, acridines, phenazines or thiazines, or phenone or quinone derivatives, e.g. camphorquinone and acetophenone. A preferred photoinitiator system for room temperature light polymerization of a macromer according to the present invention consists of a combination of camphorquinone and one or more tertiary amines such as phenylglycine. When polymerization is to take place in the absence of light, there can be used a redox system such as a peroxide (e.g. acetyl, benzoyl, cumyl or tert-butyl), a hydroperoxide (e.g. cumyl or tert-butyl), a perester (e.g. tert-butyl perbenzoate), an acyl alkylsulfonyl peroxide, a dialkyl peroxydicarbonate, a diperoxyketal, a ketone peroxide or an azo compound (e.g. 2,2'-azobisisobutyronitrile), possibly in association with at least a compound such as N,N-dimethyltoluidine. Preference shall be given to redox systems which are able to polymerize the macromers of the present invention at a temperature not above about 40°C within a reasonable period of time suitable for implantation into a patient. Possibly, a combination of a polymerization photoinitiator and a redox system can also be used, leading to a so-called « dual curing » system combining both polymerization mechanisms. The amount of such polymerization initiators and/or redox systems to be incorporated into the biologically-active formulations of this invention is an effective amount for achieving macromer polymerization at the desired rate and is well known to those skilled in the art of light or radical polymerization methods.

[0037] The manufacture of the biologically-active formulations of this invention shall be performed according to methods well known to those skilled in the art, namely by efficiently mixing the various components of the formulation by suitable means, depending on the equipment available, for a sufficient period of time to achieve a substantially homogeneous mixture. In order to avoid premature polymerization of the formulation, it is usually advisable to incorporate the polymerization initiator and/or redox system only at the very end of the mixing procedure, i.e. shortly before using the formulation for the preparation of an implant. For the obtention of an homogeneous mixture, it may be advisable to pre-mix some of the formulation additives, such as for instance the therapeutic agent(s), the protein delivery system and/or the degradable biocompatible porosity-inducing component, prior to their incorporation into the biodegradable crosslinkable prepolymer (i.e. polyester, polyorthoester or polyacetal) or macromer.

[0038] The present invention further provides therapeutically-active biodegradable implants manufactured by polymerizing a biologically-active formulation (i.e. including a crosslinkable macromer) such as previously described. Biodegradation of the said implants occurs at the linkages between the different region(s) of the crosslinkable multifunctional macromer of the present invention and results in nontoxic fragments that constitute safe chemical intermediates in the body of a mammal such as a human, a horse, a dog, a bovine or the like. For this reason, the present invention is useful for the preparation of load-bearing and non load-bearing implants such as bones, cartilage, vertebral discs, mandible prostheses and the like. Accordingly the present invention also provides a method for preparing a therapeu-

tically-active biodegradable implant including the steps of (a) combining at least one biodegradable crosslinkable prepolymer having at least two polymerizable end groups, such as previously described, with at least one biologically-active ingredient (such as described hereinabove) and optionally with at least one additive selected from biologically-active component delivery systems, biocompatible unsaturated functional monomers, biocompatible degradable porosity-inducing components and polymerization initiators, (b) implanting the said combination into the body of a mammal, such as a human, a horse, a dog, a bovine or the like at a place suitable for growth and (c) exposing the said implanted combination to conditions suitable for crosslinking the biodegradable crosslinkable multifunctional prepolymer at a temperature not exceeding about 40°C. The said method is widely applicable to a range of bone implants, as mentioned hereinabove. Namely, it is applicable to both load-bearing applications (such as for instance a hip implant) and non load-bearing applications (such as for instance a cronal fracture) for curing both self- and non self-healing bone defects.

[0039] Furthermore, the present invention provides a method for repairing bone defects by implanting a bone repair formulation into the body of a mammal, namely a human or a domesticated animal such as a horse, a dog, a bovine or the like, at a place suitable for bone growth (e.g. a bone cavity), the said bone repair formulation comprising at least one biodegradable crosslinkable multifunctional prepolymer having at least two polymerizable end groups, such as previously described, and at least one biologically-active ingredient and optionally at least one additive selected from biologically-active component delivery systems, biocompatible unsaturated functional monomers, biocompatible degradable porosity-inducing components, biopolymers and polymerization initiators, and further crosslinking *in situ* the said bone repair formulation under the influence of light and/or a temperature not exceeding about 40°C. The detailed nature of the ingredients of the bone repair formulation is as disclosed in the previous part of this application. The crosslinking step of the bone defect repair method of the present invention may be carried out by any acceptable means known in the art, such as placing the bone site to be repaired, including the implanted bone repair formulation, in the presence of a device such as a lamp providing a light with a wavelength of at least about 300 nm or of a source of moderate heat (ensuring a temperature not exceeding about about 40°C) for a period of time sufficient to achieve a substantially complete polymerization/crosslinking of the prepolymer/macromer. Completeness of polymerization can be monitored and followed by conventional means well known to those skilled in the art such as, for instance, differential scanning calorimetry and/or rheometry. Similarly, the success of this therapeutic implant and the corresponding bone defect repair will be evaluated and followed by suitable means well known in the art, such as macroscopic observation, scintigraphy and/or histology.

[0040] The present invention will now be explained in further details by reference to the following examples, which are provided for illustrative purposes only and without any limiting intention.

EXAMPLE 1 - preparation of a polyester diol prepolymer

[0041] Equimolar amounts (0.05 mole) of recrystallized D,L-lactide (7.2 g) and distilled ε-caprolactone (5.7 g) was added into a polymerization tube. 0.005 mole of 1,6-hexanediol was then added to the mixture, together with 0.00917 g zinc acetate as a catalyst. The polymerization tube was then immersed into carbon dioxide ice at -78°C, evaucated and sealed while still under vacuum. Polymerization was then performed by placing the said tube into a thermostatic bath at 140°C for 52 hours, thus resulting in 13.49 g of a poly(DL-lactide-co-ε-caprolactone)-co-hexanediol containing 0.005 alcohol end groups per macromolecule. This polymer was characterized using ^{1}H- and ^{13}C-NMR spectroscopy, differential scanning calorimetry and gel permeation chromatography, showing an average molecular weight of about 2,700.

EXAMPLE 2 - preparation of a polyester bis-methacrylate

[0042] The polyester diol prepolymer obtained in example 1 was dissolved in 27 ml of freshly distilled methylene chloride. Then 2.3 g distilled methacrylic anhydride (0.015 mole) and 0.275 g dimethylaminopyridine were added and reaction was allowed to perform for 96 hours at room temperature, thus resulting in a poly(DL-lactide-co-ε-caprolactone)-co-hexanediol capped at both ends with methacrylate groups. This polymer was characterized using ^{1}H- and ^{13}C-NMR spectroscopy, differential scanning calorimetry and gel permeation chromatography.

EXAMPLE 3 - preparation of a formulation for bone defect repair

[0043] 0.2546 g of the polyester bis-methacrylate obtained in example 2 was mixed together with 0.2562 g of demineralized bone powder, 4.42 mg of DL-camphorquinone and 2.54 mg N-phenylglycine until a composite paste (with a viscosity such that it is deformable at moderate temperature by hand or by a syringe) is obtained (all components, except bone powder, being previously sterilized by means of ethylene oxide). This paste was then inserted into a cranial defect experimentally created in a dog. The animal study described herein was conducted according to methods ap-

proved by regulatory authorities. The composite was then crosslinked by exposure to visible light (blue light, maximum wavelength of 470 nm), using a dental lamp (Dental Visible Light Curing Unit, available from Minnesota Mining Company, United States) for a period of 20 seconds. *In vivo* histological evaluation of the defect repair was conducted six months after operation and is considered to be satisfactory.

EXAMPLE 4 - Preparation of a bismethacrylate polyorthoester

a) preparation of polyorthoester-diol

[0044] While maintaining anhydrous conditions, 1,6-hexanediol (112.85 g, 0.955 mole) and 1.8 l of tetrahydrofuran (distilled over calcium hydride) were placed into a 5 l three-necked flask equipped with an overhead stirrer, an argon inlet tube and a condenser on a trap. The mixture was stirred until all solids have dissolved; then 3,9-bis(ethylidene 2,4,8,10- tetraoxaspiro[5,5]undecane) (182.44g, 0.859 mole) is added. Polymerization was initiated by the addition of 0.5 ml of a 20 mg/ml solution of *p*-toluenesulfonic acid in tetrahydrofuran. The polymerization temperature rapidly rose to the boiling point of tetrahydrofuran and then gradually decreased. Stirring was continued for about 2 hours, then 1 ml of a triethylamine stabilizer was added and the reaction mixture very slowly poured with vigorous stirring into about 5 *gallons* of methanol containing 10 ml of triethylamine. The precipitated polymer was collected by vacuum filtration and dried in a vacuum oven at 60°C for 24 hours, thus yielding 265 g (90%). A molecular weight of 3,500 was determined by gel permeation chromatography.

b) Preparation of a bismethacrylate polyorthoester

[0045] The polyorthoester (265 g) obtained in example 4a was dissolved in dichloromethane (1.8 l, distilled over calcium hydride) in a 5 l two-neck flask. Triethylamine (6 g, 0.059 mole) was added, then methacryloyl chloride (10 g, 0.0956 mole) was added dropwise while keeping the reaction temperature at 0°C. The reaction mixture was stirred for 24 hours and the resulting polymer was washed with 0.1 M H_2SO_4, then extracted three times with an aqueous 8% $NaHCO_3$ solution and finally precipitated in methanol. The precipitated polymer was collected by filtration and dried at reduced pressure for 24 hours, yielding an amount of 258g (96%).

EXAMPLE 5 - preparation of a bismethacrylate polyester

[0046] While maintaining anhydrous conditions, recrystallized D,L-lactide (0.7206 g, 0.005 mole) and 5 ml of tetrahydrofuran distilled over calcium hydride are placed into a 25 ml two-necked flask equipped with an argon inlet tube. The mixture was stirred untill all D,L-lactide was dissolved. In another 25 ml two-necked flask equipped with a rubber septum, 1,6-hexanediol (0.0295 g, 0.00025 mole, previously dried at 60°C at reduced pressure over P_2O_5) and a potassium tertiary butoxide initiator (0.0561 g, 0.0005 mole) were dissolved in 5 ml distilled tetrahydrofuran. This mixture was stirred for 15 minutes. The initiator solution was then injected into the monomer solution through the rubber septum by using a syringe. Polymerization was performed at room temperature and, after 5 minutes, was terminated by adding an excess of methacryloyl chloride (0.52 g, 0.005 mole). The resulting polymer solution was washed with a 1 M H_2SO_4 aqueous solution, extracted three times with a 8% $NaHCO_3$ aqueous solution, dried over $MgSO_4$, precipitated in pentane and dried under reduced pressure for 24 hours. 0.7684 g (98% yield) of a polyester-bismethacrylate was thus obtained. The polymer was characterized using ^1H- and ^{13}C-NMR spectroscopy, differential scanning calorimetry and gel permeation chromatography (showing an average molecular weight of 3,136).

EXAMPLE 6 - preparation of a polyester-diol containing a poly(ethylene oxide) sequence.

[0047] Recrystallized D,L-lactide (0.1 mole, 14.41 g) was added into a polymerization tube. 5 g of a poly(ethylene oxide)-diol, (average molecular weight 1,000, 0.005 mole, previously dried at 60°C under reduced pressure for 24 hours over P_2O_5) was added to the tube together with as a zinc acetate catalyst (0.0183 g, 0.0001 mole). The polymerization tube was then immersed into carbon dioxide ice at-78°C, evacuated and sealed under reduced pressure. Polymerization was then performed by placing this polymerization tube in a thermostatic bath at 140°C for 52 hours, thus resulting in 19.41 grams of poly(D,L-lactide)-co-poly(ethylene oxide)-co-poly(D,L-lactide)-diol containing 0.01 mole (0.17 g) of alcohol end groups per macromolecule. The polymer was characterized using ^1H- and ^{13}C-NMR spectroscopy, differential scanning calorimetry and gel permeation chromatography, showing an average molecular weight of 3,880. The alcohol end groups of this polymer were then converted into methacrylate end groups according to the procedure described in example 2.

EXAMPLE 7 - preparation of a bone repair formulation containing a methacrylamide modified gelatin.

[0048] 0.2546 g of the polyester bismethacrylate obtained in example 2 was mixed together with 0.2546 g of methacrylamide modified gelatin particles (having a particle size in the range of 100 to 150 μm), 4.42 mg DL-camphorquinone and 2.54 mg N-phenylglycine until a composite paste (with a viscosity such that it is deformable at moderate temperature by hand or by a syringe) is obtained. The synthesis of a methacrylamide modified gelatin is described by A. Van Den Bulcke et al., *Biomacromolecules* (2000)1:31-38. This paste is then injected in a cast and hardened by crosslinkage by irradiation under the same conditions as described in example 3.

EXAMPLE 8 - preparation of a bone repair formulation containing calcium phosphate powder and bone morphogenetic proteins.

[0049] 0.2546 g of the polyester methacrylate obtained in example 2 was mixed together with 0.2546 g of a calcium phosphate powder (having a particle size in the range of 100 to 150 μm), 4.42 mg DL-camphorquinone, 2.54 mg N-phenylglycine and 0.025 g of freeze dried gelatin powder (having a particle size in the range of 100 to 150 μm) containing 10 μg bone morphogenetic proteins, until a composite paste (with a viscosity such that it is deformable at moderate temperature by hand or by a syringe) is obtained. This paste is injected in a cast and hardened by crosslinkage by irradiation under the same conditions as described in example 3.

EXAMPLE 9 - preparation of a branched polyester-tetrol prepolymer.

[0050] Equimolar amounts (0.05 mole) of recrystallized D,L-lactide (7.2 g) and distilled ε-caprolactone (5.7 g) were added into a polymerization tube. Pentaerythritol (0.005 mole, 0.6807 g, previously dried at 60°C under reduced pressure for 24 hours over P_2O_5) was added to the tube together with a zinc acetate catalyst (0.0183 g, 0.0001 mole). The polymerization tube was then immersed into carbon dioxide ice at -78°C, evacuated and sealed under reduced pressure. Polymerization was then performed by placing this polymerization tube in a thermostatic bath at 140°C for 52 hours, thus resulting in 13.58 g of a poly(D,L-lactide)-co-poly(ε-caprolactone)-pentaerythritol-tetrol containing 0.01 mole (0.17 g) of alcohol end groups per macromolecule. The polymer was characterized using ^{1}H- and ^{13}C-NMR spectroscopy, differential scanning calorimetry and gel permeation chromatography, showing an average molecular weight of 2716.

EXAMPLE 10 - preparation of a branched polyester methacrylate.

[0051] The alcohol end groups of the branched polyester-tetrol of example 9 were converted into methacrylate end groups according to the procedure described in example 2.

Claims

1. A composition suitable for preparing a therapeutically-active biodegradable implant, comprising at least one crosslinkable multifunctional prepolymer having at least two polymerizable end groups and at least one biologically-active component, the said composition having a viscosity such that it is deformable at a temperature between 0°C and 60°C, more preferably between 15°C and 40°C into a three-dimensional shape and being hardenable by crosslinkage within the said temperature range.

2. A composition according to claim 1, wherein the average number molecular weight of the said crosslinkable multifunctional prepolymer is in the range of 200 to 20,000.

3. A composition according to claim 1 or claim 2, wherein the said crosslinkable multifunctional prepolymer comprises (1) at least one biodegradable region and (2) at least one polymerizable region and optionally (3) a hydrophilic region.

4. A composition according to claim 3, wherein the hydrophilic region of the said crosslinkable multifunctional prepolymer is a polyethylene glycol.

5. A composition according to claim 3 or 4, wherein the biodegradable region of the said crosslinkable multifunctional prepolymer is a predominantly amorphous region.

6. A composition according to any of claims 3 to 5, wherein the biodegradable region of the said crosslinkable multifunctional prepolymer comprises a polyacetal sequence.

7. A composition according to any of claims 3 to 5, wherein the biodegradable region of the said crosslinkable multifunctional prepolymer comprises a polyothoester sequence.

8. A composition according to any of claims 3 to 5, wherein the biodegradable region of the said crosslinkable multifunctional prepolymer comprises a polyester sequence resulting from copolymerizing a mixture of lactones wherein none of the lactone comonomers is present in the resulting polyester sequence in a molar proportion above 70%, or a polyorthoester sequence.

9. A composition according to any of claims 3 to 8, wherein the polymerizable region contains ethylenic and/or acetylenic unsaturations.

10. A composition according to any of claims 1 to 9, further comprising at least one additive selected from biologically-active component delivery systems, biocompatible unsaturated functional monomers, biocompatible degradable porosity-inducing components and polymerization initiators.

11. A composition according to claim 10, wherein the biologically-active component delivery system comprises demineralized bone powder, resorbable calcium phosphate-based particles, hydroxyapatite powder or coral powder.

12. A composition according to claim 10 or claim 11, wherein the biocompatible degradable porosity-inducing component is selected from gelatine, fibronectin, vitronectine, a carbohydrate such as hyaluronic acid, dermatan sulphate, chondroitinsulphate, or derivatives of said biopolymers containing polymerizable side groups and/or porous polymeric particles.

13. A composition according to any of claims 1 to 12, wherein the biologically-active component is selected from bone repair promoters, antimicrobial agents, proteins, peptides, hormones, carbohydrates, antineoplastic agents, antiangiogenic agents, vasoactive agents, anticoagulants, immunomodulators, cytotoxic agents, antiviral agents, antibodies, neurotransmitters, oligonucleotides, lipids, plasmids, DNA and diagnostic agents.

14. Use of a composition according to any of claims 1 to 13 for the preparation of a therapeutically-active biodegradable implant.

15. Use according to claim 14, wherein the therapeutically-active biodegradable implant is a bone implant.

16. A biodegradable crosslinkable multifunctional prepolymer having at least two polymerizable end groups, comprising (1) at least one biodegradable region, (2) at least one polymerizable region and optionally (3) a hydrophilic region, wherein the said biodegradable region is a predominantly amorphous region.

17. A biodegradable crosslinkable multifunctional prepolymer according to claim 16, wherein the predominantly amorphous biodegradable region is a polyester, polyorthoester or polyacetal sequence.

18. A biodegradable crosslinkable multifunctional prepolymer according to claim 16 or claim 17, wherein the polymerizable region contains ethylenic and/or acetylenic unsaturations.

19. A biodegradable crosslinkable multifunctional prepolymer according any of claims 16 to 18, wherein the hydrophilic region is a polyether polyol with two or more hydroxyl groups derived from polyethylene glycol or a copolymer of ethylene oxide and propylene oxide.

20. A biodegradable crosslinkable multifunctional prepolymer according to any of claims 16 to 19, **characterized in that** the polymerizable region contains acrylamide or methacrylamide groups obtained by reacting the terminal hydroxy groups of a precursor of the biodegradable region with an unsaturated azlactone.

21. A process for manufacturing a biodegradable crosslinkable multifunctional polyester prepolymer having at least two polymerizable end groups, comprising polymerizing a lactone or copolymerizing a mixture of lactones at a temperature between 120°C and 180°C in the presence of at least a polyol, and of at least a lactone polymerization catalyst and, possibly after a step for removing the catalyst from the polymer obtained, reacting the latter with a

monomer containing at least one ethylenic or acetylenic unsaturation.

22. A process for manufacturing a biodegradable crosslinkable multifunctional polyorthoester prepolymer having at least two polymerizable end groups, comprising polymerizing a diketene acetal or copolymerizing a mixture of diketene acetals in the presence of at least one polyol, and of at least a ketene acetal polymerization catalyst and, possibly after a step for removing the catalyst from the polymer obtained, reacting the hydroxyl end groups of the latter with a monomer containing at least one ethylenic or acetylenic unsaturation.

23. A process for manufacturing a biodegradable crosslinkable multifunctional polyacetal prepolymer having at least two polymerizable end groups, comprising polymerizing a divinylether derivative or copolymerizing a mixture of divinylether derivatives in the presence of at least one polyol and of at least a vinylether polymerization catalyst and, possibly after a step for removing the catalyst from the polymer obtained, reacting the hydroxyl end groups of the latter with a monomer containing at least one ethylenic or acetylenic unsaturation.

24. A process according to claim 21, wherein the polyol is used in a molar ratio, with respect to the lactone(s) of not more than 1 :100, preferably no more than 1 :10.

25. A process according to claim 22 or 23, wherein the molar ratio of the alcohol groups to the ketene acetal or vinylether is in a controlled excess of between 0.1% and 30%.

26. A process for manufacturing a biodegradable crosslinkable multifunctional prepolymer having at least two polymerizable end groups, comprising anionically polymerizing a lactone or copolymerizing a mixture of lactones at a temperature below 30°C, in the presence of an aprotic solvent and further in the presence of at least an alcaline metal alkoxide, an anionic polymerization catalyst and a monomer containing at least one ethylenic or acetylenic unsaturation.

27. A method for making a therapeutically-active biodegradable implant including the steps of (a) combining at least one specific biodegradable crosslinkable multifunctional prepolymer having at least two polymerizable end groups, together with at least one biologically-active component and optionally at least one additive selected from bioactive component delivery systems, biocompatible unsaturated functional monomers, biocompatible degradable porosity-inducing components, biopolymers and polymerization initiators so as to provide a viscous but still flowable liquid mixture, (b) implanting the said mixture into the body of a mammal at a place suitable for growth and (c) exposing the said implanted mixture to conditions suitable for crosslinking the biodegradable crosslinkable multifunctional prepolymer and optionally the biocompatible unsaturated functional monomers within a reasonable period of time at a moderate temperature.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 00 20 1198

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.7)
X	US 5 108 755 A (DANIELS ALMA U ET AL) 28 April 1992 (1992-04-28) * abstract * * column 1, line 7-17 * * column 3, line 64-68 * * column 4, line 60-68 * * column 5, line 10-19,47-62 * * column 9, line 58-65 * ---	1-3,6,7, 10,13, 14,16, 17,21, 22,26,27	A61L27/16 A61L27/54 C08G63/91 C08F290/06
X	US 5 837 752 A (SHASTRI VENKATRAM R ET AL) 17 November 1998 (1998-11-17) * abstract * * column 3, line 21-42 * * column 4, line 33-62 * * column 5, line 35-52 * * column 6, line 44 - column 7, line 2,65-68 * * column 9, line 25-67 * ---	1-4, 9-16,19, 20,27	
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The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	4 September 2000	Böhm, I

CATEGORY OF CITED DOCUMENTS

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ANNEX TO THE EUROPEAN SEARCH REPORT ON EUROPEAN PATENT APPLICATION NO. EP 00 20 1198

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